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A case of a 45,X,46,X+mar male phenotype mosaic Turner syndrome with a mixed gonadal germ cell tumor

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Abstract:

Turner syndrome is a congenital condition affecting 1 in every 2500 female live births. This condition is characterized by complete or partial loss of the X chromosome. They commonly present with normal female external and internal genitalia and may develop hypogonadism and streak ovaries later in life. We describe an unusual presentation of a case of Turner syndrome – a 31-year-old Filipino with male phenotype mosaic Turner syndrome, with 46,X,+mar[46]/45,X[4] chromosome, presenting with ambiguous genitalia and a pelvoabdominal mass. The patient underwent exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, tumor debulking (gonadectomy) appendectomy, omentectomy, identification and inspection of bilateral ureters and bladder, gonioscopy and biopsy of the urogenital cavity (bladder vs. vagina). Histopathology revealed a mixed gonadal tumor, consisting of 70% yolk sac tumor, and 30% dysgerminoma. The patient eventually succumbed to postoperative complications. Postmortem fluorescence-*in situ* hybridization revealed a 46,X,+mar[46]/45,X,[4].ish der (Y) (DYZ3+), a marker of chromosome Y origin, consistent with a mosaic type Turner syndrome, associated with increased risk for gonadal malignancy.

Keywords:

Dysgerminoma, mixed germ cell tumor, mosaic Turner syndrome, mosaicism, yolk sac tumor

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Introduction

Disorders of sex development (DSD) include a wide range of congenital anomalies among the chromosomal, gonadal, and genital characteristics that define the sexual differentiation.[1] DSD affects 1 in every 4000–5000 live births and is mainly due to genetic aberrations in fetal sex differentiation.[2]

Disorders of sexual differentiation include common and uncommon entities and may be further classified based on a primary genetic defect. Mixed gonadal dysgenesis results from a numerical sex chromosome abnormality which leads to abnormal gonadal development.

Patients with gonadal dysgenesis are found to have an increased risk of developing gonadal tumors.[3] Patients with 45,X/46,XY mosaicism or those with a fragment of Y chromosome (45,X/46,X+mar) are at increased risk of developing gonadal tumors. In a systematic review in 2019, a karyotype of 45, X accounts for 60% of cases of germ cell tumors among patients with dysgenetic gonads.[4]

We report a case of a mixed gonadal tumor, containing yolk sac tumor, and dysgerminoma, which developed in a 31-year-old Filipino adult with 46X,+mar[46]/45,X[4] karyotype who also presents with ambiguous genitalia. Postmortem fluorescence-*in situ* hybridization revealed a 46,X,+mar[46]/45,X[4].ish der (Y) (DYZ3+), a marker of

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chromosome Y origin, consistent with a mosaic type Turner syndrome. This is a rare case due to late recognition of gonadal dysgenesis, with the usual age of diagnosis being before adolescence.

Case Report

This is a case of a 31-year-old Filipino adult, raised as male, who sought consult due to urinary retention associated with a pelvoabdominal mass. Four months before the consult, the patient complained of a palpable pelvoabdominal mass over the left lower quadrant, with associated occasional hypogastric pain, and feeling of incomplete bladder emptying. In a span of 2 months, the patient noted the abrupt increase in the size of the said mass, now reaching the xiphoid area, and persistence of the abovementioned signs and symptoms. One month before consult, the patient complained of increased severity of the abdominal pain, now radiating to the left lower quadrant. The patient sought a consult at another institution, wherein a whole abdominal computer tomography was done, revealing a large pelvoabdominal mass occupying the mid to lower abdomen, measuring approximately 12.04 cm × 11.98 cm × 13.79 cm, suggestive of cryptorchidism with probable development of testicular germ cell tumor from undescended testis. There is also noted bilateral obstructive uropathy, and a developed penis with an empty scrotal sac. The working impression at that time was cryptorchidism, with probable development of testicular germ cell tumor from undescended testis, with bilateral obstructive uropathy from the pelvoabdominal mass. The patient was advised surgery; however, the patient was discharged against medical advice because they wanted to seek a second opinion. One week before admission, there was an increase in the severity of the urinary and hypogastric symptoms; hence, the patient sought consult at our institution. The patient was subsequently admitted under the urology service.

The past medical history of the patient is unremarkable and he denies any heredofamilial diseases. The patient is a 31-year-old adult college graduate.

For the sexual history, the patient developed secondary sexual characteristics at the age of 11, at par with age, however, with a noted empty scrotal sac. The patient's coitarche at 16-year-old and had two sexual partners, one previous female sexual partner and a current female sexual partner. The patient also complains of persistent erectile dysfunction.

On physical examination, the patient has a weight of 49 kg and a height of 139 cm (body mass index: 25.4), with an arm span of 130 cm. Examination of the breasts showed Tanner Stage 2 breasts with breast budding, widely spaced nipples with palpable breast tissue under the nipple. Examination of extremities showed tan-colored skin, with sparse, thin curly hair at the axillary area. The pubic hair was at Tanner Stage IV. The patient also had a Grade II pitting bipedal edema [Figure 1].

Abdominal examination showed a globularly enlarged abdomen, with an abdominal girth of 82 cm, with central dullness and peripheral tympanism. There is a palpable pelvoabdominal mass measuring 20 cm × 20 cm × 17 cm, solid with an irregular border, slightly movable, tender on deep palpation, with no fluid wave or shifting dullness. Examination of the external genitalia revealed Tanner stage 3 pubic hair. There was a cylindrical and small phallus, measuring 4 cm × 2 cm. There is also a small blind opening at the base of the phallus, measuring 0.5 cm [Figure 1].

The primary impression at this time was obstructive uropathy secondary to pelvoabdominal mass, probably testicular carcinoma, probably secondary to bilateral undescended testes, to consider ambiguous genitalia secondary to DSD. Karyotyping, tumor markers, and hormonal assays were requested. Due to urinary retention, peripheral nephrostomy tubes were placed in order to relieve renal obstruction from the pelvoabdominal mass.

Karyotyping was done at the Institute of Genetics at the National Institutes of Health using the G Banding method [Figure 2]. Chromosome analysis revealed a 46X,+mar[46]/45,X[4], mosaicism. The hormonal assessment showed elevated luteinizing hormone, elevated follicle-stimulating hormone, and

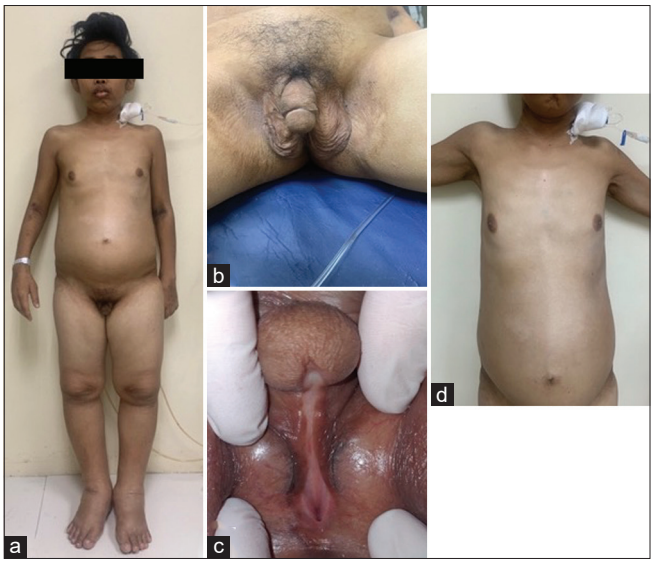

Figure 1: Phenotypic features of the case, showing (a) general body habitus showing a globular abdomen, with bilateral lymphedema, (b) Tanner Stage III for pubic hair, with sparse hair growth at the base of the phallic structure, and a 4 x 2 cm phallus with a tuft of scrotal type of skin at the base, (c) a blind opening, 0.5 cm wide, and (d) a globularly enlarged abdomen, with an abdominal girth of 82 cm

low testosterone, pointing out to a hypogonadotropic hypogonadism [Table 1]. Serum estradiol and dehydroepiandrosterone were not done due to financial constraints.

Tumor markers were done, which showed elevated beta-HCG and alpha-fetoprotein, pointing out to a probable mixed-type gonadal tumor [Table 1]. The current working impression at this time is a pelvoabdominal mass, probably a gonadal malignancy, laterality undetermined, in a patient with Turner Syndrome. Due to the said findings, the patient was transferred to the care of obstetrics and gynecology (OB-GYN) service.

The patient also underwent transrectal ultrasound requested by OB-GYN service to characterize the pelvoabdominal mass, with a primary impression of ovarian new growth, measuring 19.02 cm × 18.07 cm × 14.4 cm, with nonbenign sonologic features by IOTA Adnex scoring. There also seems to be a canal posterior to the bladder, probably representing the vagina. At this time, the primary working impression was a Gonadal malignancy probably secondary to mixed gonadal dysgenesis, Turner Syndrome, 46X,+mar[46]/45,X[4]. The patient was also referred to Psychiatry service due to suicidal thoughts and thoughts of self-harm and was started on escitalopram 10 mg at bedtime.

Table 1: Laboratory results showing serum hormonal tests and serum tumor markers

Laboratory test	Patient's result	Normal values
Testosterone	1.19 ng/mL	2.8-8.8 ng/mL
Follicle Stimulating Hormone (FSH)	88.47 mIU/mL	Men: 1.5-12.4 mIU/mL Women: Follicular: 3.5-12.5 mIU/mL Ovulatory: 4.7-21.5 Luteal: 1.7-7.7 Postmenopause: 25.8-134.8
Luteinizing Hormone (LH)	74.23 mIU/mL	Men: 1.7-8.6 mIU/mL Women: Follicular: 2.4-12.6 Ovulatory: 12-95.6 Luteal: 1.0-11.4 Postmenopause: 7.7-58.5
Beta-human chorionic gonadotropin (beta-HCG)	7.01 mIU/mL	<2.06 mIU/mL
Alpha fetoprotein	>2000 ng/mL	0.89-8.78 ng/mL
Lactate Dehydrogenase (LDH)	655 U/L	125-220 U/L

A multidisciplinary meeting and a preoperative conference was done, involving general surgery, urology, obstetrics and gynecology, internal medicine, and psychiatry. The patient subsequently underwent exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, tumor debulking (gonadectomy), appendectomy, omentectomy, identification and inspection of bilateral ureters and bladder, gonadoscopy and biopsy of the urogenital cavity (bladder vs. vagina). On laparotomy, the pelvoabdominal mass measured 20 cm × 21 cm × 18 cm, solid, with an irregular border, and with a thick capsule. It was located retroperitoneally, with adhesions to the omentum [Figures 3 and 4]. After adhesiolysis, the transverse colon was located superior to the mass, and on further dissection, the sigmoid colon was located posterior to the mass. Adhesiolysis, tumor debulking (gonadectomy), appendectomy, omentectomy, and placement of abdominal pack were done due to 20% of tumor residuals in the left pelvic area with bleeding. Intraoperative referral to urology was done to identify and inspect bilateral ureters and bladder, and endoscopy with biopsy of the slit-like structure at the penoscrotal junction. There is an elongated tubular structure on endoscopy with smooth mucosa lining the lumen. The scope was inserted up to 10 cm with noted difficulty advancing the scope after this distance. The abdominal mass, part of the omentum, retroperitoneal mass, appendix, the identified uterus, and fallopian tubes, and a sample from the endoscopy were sent to histopathology. The patient had a total of 3000 mL blood loss, and a total of six units of packed red cells

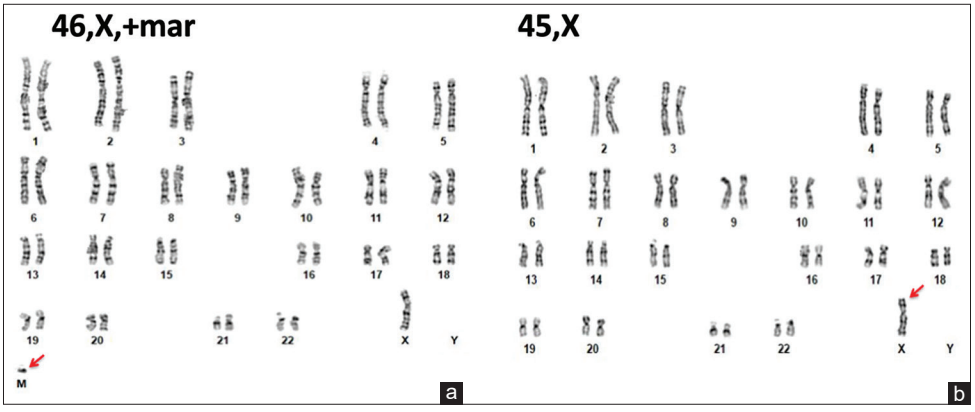

Figure 2: Karyotyping done at University of the Philippines-National Institutes of Health, showing (a) 46x,+ mar [46], mosaicism for a cell line with a marker chromosome, and (b) a cell line with loss of one X-chromosome, 45, X [4]

and six units of platelet concentrate were transfused intraoperatively.

On postoperative day 3, the abdominal pack was removed under intravenous sedation and obtained 1300 mL of serosanguinous fluid. On postoperative day 5, a whole abdominal contrast tomography scan showed distended bowel loops, involving the ascending, transverse, and proximal descending colon. Ultrasound-guided paracentesis was done, and tea-colored ascitic fluid was drained. On postoperative day 15, repeat scout film of the abdomen showed distended bowel loops. The case was referred to general surgery, with a working impression of small bowel perforation, and exploratory laparotomy under general endotracheal anesthesia was done on postoperative day 17. On opening, multiple adhesions were noted between the small bowels and the abdominal wall. The small bowels were twisted, with multiple hematomas on the mesentery. On exploration, 20 cm of the jejunum was necrotic with multiple points of rupture. Segmental resection of the small bowels, double-barrel jejunostomy, and placement of peritoneal drain was done. The culture of the fecaloid material was sent, which showed the growth of *Pseudomonas aeruginosa*. The patient was transferred to the intensive care unit (ICU). The patient was continuously monitored at the ICU; however, on postoperative day 23, the patient eventually succumbed to sepsis.

Histopathology of the abdominal mass revealed histologic features consistent with a mixed germ cell tumor. Approximately 70% of the viable tumor cells show features of yolk sac tumor, and approximately 30% of the viable tumor cells show features of dysgerminoma [Figure 5]. There were intratumoral and extratumoral lymphovascular invasion, with involvement of the omentum, bladder, fallopian tubes, and appendix.

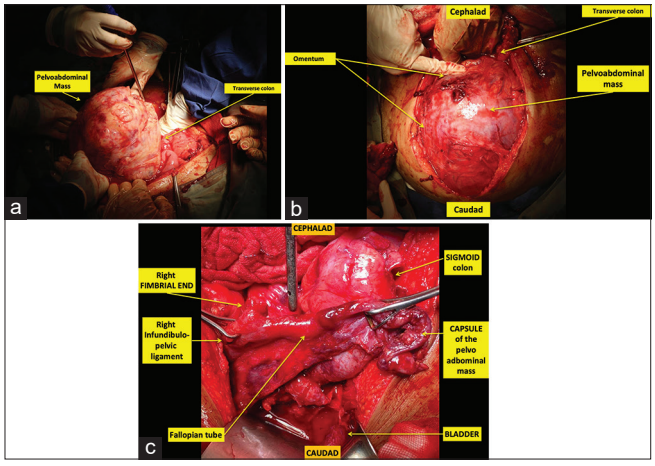

Figure 3: Intraoperative findings of the abdominal mass. (a) and (b) showing adhesions with the omentum, with omental caking and tumor implants on the appendix, and (c) showing adhesion of the mass to the fallopian tube

Postmortem fluorescence-*in situ* hybridization (FISH) was done to determine the presence of Y chromosome material, which could provide an explanation for the aggressive nature of the tumor. FISH revealed a 46, X,+mar[46]/45,X[4].ish der (Y) (DYZ3+), a marker of chromosome Y origin [Figure 6]. The marker chromosome is therefore interpreted as a derivative of chromosome Y. These findings are consistent with mosaic 45,X/46,XY. Our case is a male phenotype mosaic Turner syndrome with ambiguous genitalia, which presented with a gonadal mass revealing a mixed gonadal germ cell type tumor of yolk sac tumor and dysgerminoma component on histopathologic evaluation.

Discussion

DSD are a group of conditions characterized by atypical chromosomal, gonadal, and anatomic sexual development.[1] The clinical spectrum of these conditions is broad, manifesting as postpartum virilization, delayed or absent puberty, infertility, or indeterminate genitalia.[4]

Normal sexual differentiation begins at 6–8 weeks age of gestation and begins with the bipotential gonad. Usually, this is completed at 12 weeks of gestation and is followed by the development of the penis, and descent of the testes into the scrotal sac.[1] In 45,X/46,XY mosaicism, there is a loss of structural abnormal Y material arising through the anaphase lag during mitosis.[5] There is normal ovarian development at the beginning of fetal life, followed by a rapid loss of germ cells beginning at 22 weeks age of gestation, resulting in a streaked gonad around the time of delivery.[6] Dysgenetic gonads are characterized by variable degrees of immaturity or dysfunction, including

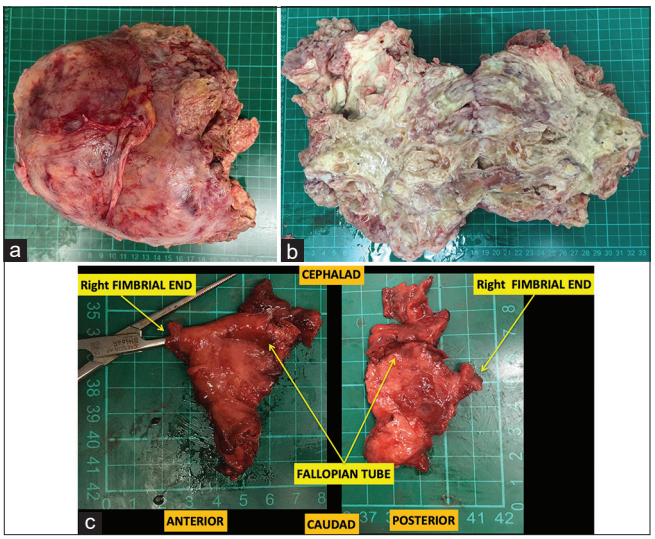

Figure 4: Pelvoabdominal mass, showing (a) gross section of the left gonadal mass, measuring 20 x 21 x 18 cm, solid, with irregular border and thick capsule; (b) cut section of the left gonadal mass, showing cystic spaces with brain-like tissues; (c) gross section of the portion of the mass adherent to the fallopian tube

suboptimal production of sex hormones. This is a random event during the cell division stage in the early fetal development of the affected individual.

Our patient presented with an initial complaint of pelvoabdominal mass, with an ambiguous genitalia, which prompted to have the patient to undergo karyotyping. Gonadal dysgenesis is a subset of DSD, characterized by incomplete or defective formation of gonads brought about by structural or numerical chromosomal anomalies, or mutation in the genes involved in the development of the gonad. The classic form of mixed gonadal dysgenesis (MGD) is 45,X/46, XY mosaicism. Patients with 45,X/46,XY mosaicism exhibit a spectrum of phenotypes, from a normal external female phenotype to females with stigmata of Turner's syndrome, to cases presenting with ambiguous genitalia, and those with an external male phenotype. Among patients with Turner syndrome, those presenting with mosaicism, streak gonads, or ambiguous genitalia have the worst prognosis, with high chance of developing the gonadal type of tumor, which can be malignant and fatal as the patient ages.[7] Our case is a Mosaic Turner syndrome with a predominantly male phenotype, presenting with a penis-like phallus but with an empty scrotal sac. On opening, there was an identified fallopian tube, with absent gonads.

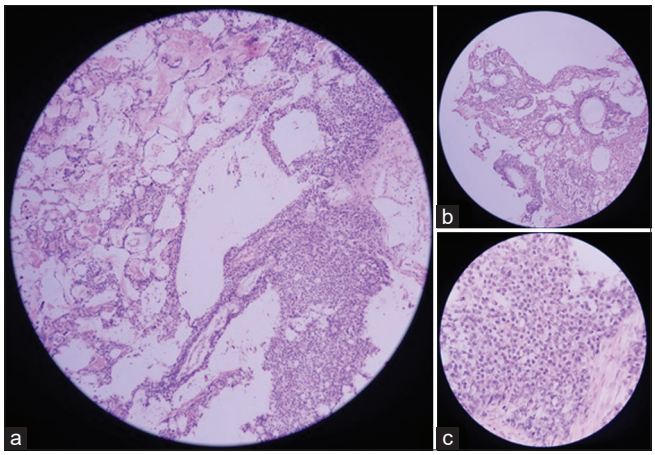

Figure 5: Histopathology slide, stained using Hematoxylin and Eosin stain (a) at 10x magnification, showing histologic features consistent with a mixed germ cell tumor with broad zones of hemorrhage, coagulative necrosis and abscess formation. (b) (at 50x magnification) Approximately 70% of the viable tumor cells shows features of a Yolk Sac Tumor with majority of tumor cells assuming a microcystic and reticular pattern. Individual tumor cells are moderately pleomorphic, with enlarged and irregularly round to ovoid nuclei, prominent nucleoli and delicate to coarsely granular chromatin. The cytoplasm is scant and granular with ill-defined borders. There are numerous Schiller-Duval bodies which are characterized by distinct fibrovascular cores forming papillae that are lined by a single layer of epithelium and are enclosed within small cystic spaces. A minor component reveals the same tumor cells forming solid sheets as well as some foci with hyaline globules and calcifications. (c) (at 50x magnification) Approximately 30% of the viable tumor cells shows features of a Dysgerminoma occurring in sheets, nests and trabeculae. Individual tumor cells are uniformly enlarged and polygonal, with irregularly ovoid nuclei, coarsely granular chromatin, prominent nucleoli and abundant clear cytoplasm with well-defined borders. The cells are admixed with numerous intratumoral lymphocytes and are separated by delicate fibrous septae. Few foci of tumor cells exhibit marked pleomorphism forming pseudoglandular structures and sheets with overlapping vesicular nuclei, punctate to prominent nucleoli and indistinct cytoplasmic borders. Mitotic activity in these regions are highest with counts up to thirteen per high power field (13/HPF) with frequent atypical mitotic figures and apoptotic debris

Aside from the ambiguous genitalia, the patient also had a pelvoabdominal mass, which turned out to be a mixed gonadal tumor consisting of a yolk sac tumor and a dysgerminoma component. Malignant mixed germ cell tumors are quite rare cancers, occurring in 8% of cases of germ cell tumors, and are very aggressive in nature. In a review by Troche and Hernandez in 1986, involving 140 patients, neoplastic transformation of abnormal gonads was common, and bilateral involvement was in 38.6% of cases.[8] In a study by Liu *et al.* in 2014 involving 102 female patients with DSD, there was an established relationship between the development of gonadoblastoma, dysgenetic gonads, and the presence of Y chromosome material.[9] The presence of MGD with a Y chromosome places the patient at the highest risk for gonadal malignancy with an incidence of 15%–25%. The risks increase with advancing age, with 50%–70% of cases developing gonadal tumors in the third decade, and up to 80% beyond it.[10] In general,

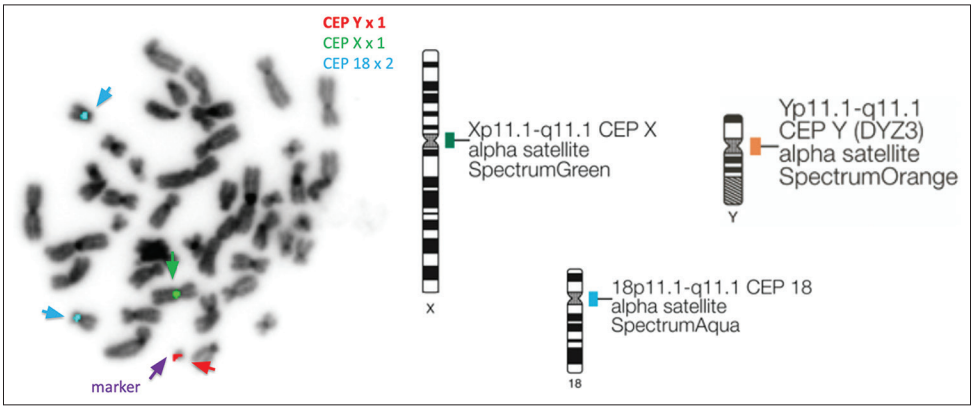

Figure 6: Post-mortem metaphase fluorescence-in-situ hybridization done at University of the Philippines-National Institutes of Health, revealing 46,X,+mar[46]/45,X[4].ish der(Y)(DYZ3+), a marker of chromosome Y origin located at the centromere

the most common malignant germ cell neoplasm associated with gonadal dysgenesis is gonadoblastoma, which is a precursor lesion that can progress into a malignant germ cell tumor. The increased risk for developing gonadal germ cell cancers is due to the hidden presence of the Gonadoblastoma Y region and is determined by the presence of Y material, mosaicism of the genotype and the degree of masculinization,[11] with 13% risk in cases of mild undervirilization, and up to 52% in cases of overt ambiguous phenotype.[12] Based on the genotypic analysis of the case, the patient has a 46,X + mar chromosome, which is a small supernumerary marker chromosome, a structurally abnormal chromosome that cannot be characterized clearly by the conventional cytogenetic banding. It is critical to clarify the characteristics and origin of the marker chromosome because they are related to the phenotype and pathologic phenomenon. Identifying the presence of Y-chromosomal material is imperative since these cases have an increased risk of gonadoblastoma deriving from the streak gonads.[13] The patient sought a consult already late at 31 years old, with a huge pelvoabdominal mass which turned out to be a mixed gonadal tumor with a yolk sac tumor and dysgerminoma component. Postmortem FISH was done, revealing a 46,X,+mar[46]/45,X[4].ish der (Y) (DYZ3+), a marker of chromosome Y origin. These findings are consistent with mosaic 45,X/46, XY, which is associated with mosaicism and ranges from infants with ambiguous genitalia, to females with Turner syndrome, hypospadias and gonadal dysgenesis, as well as sterile male phenotypes. This also explains the aggressive nature of our case - a male phenotype mosaic Turner syndrome with ambiguous genitalia, who presented with a gonadal mass, which turned out to be a mixed gonadal type tumor of yolk sac tumor and dysgerminoma component on histopathologic evaluation. Early identification of mosaicism and Y chromosome would have been crucial and life-saving since prophylactic gonadectomy may be done before the malignant transformation of gonads. Early identification of DSDs, therefore, is important, and early consultation should be facilitated.

Multispecialty management should also be done since patients with DSDs can have a wide array of symptoms. Furthermore, these patients have issues with gender identity, hence emphasizing the need for psychosocial support for these patients. In our case, the patient presented with ambiguous genitalia but was reared as male. On knowledge of the karyotyping results, the patient developed a combative behavior and developed suicidal ideations, prompting referral to psychiatry service. Multiple subspecialties were asked to intraoperatively assess the patient, including general surgery service, to aid in the resection of the pelvoabdominal mass, and urology service to assess the blind opening that was found on the base of the phallus. The blind opening at the base of the phallus was a persistent urogenital sinus.

Conclusion

Patients with Turner syndrome with mosaic chromosomes and features of masculinization are at increased risk of developing gonadal cell tumors. The development of gonadal cell malignancy increases with age, hence the need for early identification of these patients for surveillance. Patients with mosaic Turner syndrome should be screened for the presence of Y chromosome as they are at increased risk of developing malignant germ cell tumors. They should be offered prophylactic gonadectomy to prevent malignant sequelae.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Regrine Bolando Lagarteja - involved in conceptualization, data curation, writing original draft, visualization.

Brenda Bernadette Bautista -Zamora- involved in conceptualization, writing- review and editing, visualization, and supervision.

Christian A. Canoy - involved in conceptualization, investigation, provision of study resources.

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Conflicts of interest

There are no conflicts of interest.

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